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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO
08/818,534	03/14/1997	WILFRED H. NELSON	3922	9647

7590 05/07/2002

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EXAMINER
HINES, JANA A

ART UNIT	PAPER NUMBER
1645	32

DATE MAILED: 05/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/818,534	Applicant(s) NELSON ET AL.	
	Examiner Ja-Na A Hines	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2 and 9-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Amendments have been entered as filed on January 15, 2002. Claims 9 and 12 have been amended. Claims 2 and 9-15 are pending in this office action.

Drawings

2. Applicant is required to submit a proposed drawing correction in reply to this Office action. Applicants must submit proposed drawing corrections in response to the requirement in the office action.

Withdrawal of Rejections

3. The rejection of claims 2, 9-11 and 13 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicants amendments and arguments.

a) The rejection of claims 2, 9-12 and 14 under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. (US 4,487,198) in view of Herron et al.

b) The rejection of claims 2, 9-12 and 14 under 35 U.S.C. 103(a) as being unpatentable over Taracha et al., in view of Nelson et al. (US 4,487,198).

c) The rejection of claims 13 and 15 under 35 U.S.C. 103(a) as being unpatentable over Taracha et al., in view of Nelson et al. (US 4,487,198) and in further view of Muller (US Patent 5,126,244).

d) The rejection of claims 13 and 15 under 35 U.S.C. 103(a) as being unpatentable over Nelson et al., in view of Herron et al., in further view of Muller (US Patent 5,126,244).

e) The rejection of claims 13 and 15 under 35 U.S.C. 103(a) as being unpatentable over Chadha et al., in view of Herron et al., in further view of Muller (US Patent 5,126,244).

New Grounds for Rejection
Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 2, 9-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "having at least 200 fold immobilized antibodies in excess of target antigen" in claims is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Because one could not know whether there was at least 200 fold immobilized antibodies in excess of the target antigen, unless one knew how many antigens were present in the sample and one would not how many antigens were present in the sample before the method of detection was performed, the tem is relative. Thus the metes and bounds of the term cannot be readily determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 12, 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Nelson et al., (US Patent 08/818,534). Nelson et al., teach a system for detecting the presence of a specific microorganism in a sample having a means for contact the sample with a medium; a means for irradiating and a means for comparing the induced spectrum to detect the presence of the microorganism. Figure 1 shows the a slide wherein sample is contained which is means for contacting the sample with a medium; a laser as a means for irradiating the sample to produce laser light of 242-257 nm to produce a resonance enhanced Raman backscattered energy spectrum; and a means for comparison as encompassed by a library of spectra will be obtained and be rapidly scanned by a computer on the basis of resonance Raman spectra (col. 5-6 lines 64-2).

The intended use of the recited components within the system is not viewed as having structural limitations. There is no requirement for the presence of the a solid phase comprising immobilized antibodies which specifically bind to a characteristic cell surface antigen on the microorganism to form an antigen-antibody complex, thereby immobilizing the microorganism on the solid phase, the solid phase antibodies being at least 200 fold in excess of antigen, the antibodies emitting essentially no response Raman spectra that interfere with the resonance Raman spectra of said microorganism

when irradiated with a laser light of 242-257nm, thus the solid phase is not a required component of the system. Only the actual components, i.e., the means for contacting said sample with a medium, a means for irradiating and a means for comparing the induced spectrum are considered to have structural limitations. A structural difference between the claimed invention and the prior art needs to exist in order to patentably distinguish the claimed invention from the prior art, however the prior art structures are capable of performing the intended use, thus it meets the claim.

Thus, Nelson et al., teach a system for detecting the presence of a specific microorganism in a sample comprising a means for contacting the sample with a medium, a means for irradiating and a means for comparison.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 2, and 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. (US 4,487,198) in view of Tarcha et al., (US Patent 5,266,498).

Nelson et al. (US 4,487,198), teach an apparatus and a method of detection and identification of bacteria by means of ultra-violet excited resonance Raman spectra. The method uses the emitted light energy, which is resonance enhanced Raman scattering and is measured as backscattered energy where the energy processed produces spectra that are characteristic of the bacteria (abstract). The method comprises exciting taxonomic markers in a bacterium with ultra violet light as a lower

resonance enhanced Raman back scattered energy; converting the energy to correspond to the taxonomic markers; and displaying the spectra such that the bacterium may be detected and identified (col. 6 lines 43-56). Nelson et al., teach an effective range of use being 190-260nm (col. 5 lines 10-15), and further showed five different types of bacteria being excited at 242 nm (col. 5 lines 21-22). Nelson et al., teach the irradiation of the solid phase occurs between 242-257nm to produce a resonance enhanced Raman backscattered energy, as claimed by the instant claims. The resonance Raman spectra exhibits differences in the composition in the organism, nucleic acids, proteins and other markers are major contributors to the spectra reported (col. 5 lines 22-27). It is well known in the art that bacterial cells were immobilized on quartz plates by means of polylysine. The test samples were suspensions of bacterial cultures and other microorganisms can be embodied in any biologically acceptable carrier or medium (col. 6 lines 35-40). Figures 2-8 teach the excitation of *Bacillus subtilis, Pseudomonas fluorescens, Staphylococcus epidermidis, Enterobacter cloacae*, and *Escherichia coli*. However, Nelson et al., does not teach the immobilization of analyte with antibodies attached to a solid phase.

Tarcha et al., (US Patent 5,266,498) teach the use of Raman light scattering as a means of detecting or measuring the presence of a labeled specific binding member avoids previous drawbacks in the art (col. 3 lines 15-20). The method teaches assaying an analyte in a test sample by first combining the test sample with a specific binding pair having affinity for the analyte being assayed, wherein the Raman spectra of the resultant is measured (col. 5 lines 56-63). Tarcha et al., teach the attachment of specific binding members, i.e., antibodies (col. 8 lines 45-55). Example 6 teaches dye-

antibody conjugates and Raman readout in a sandwich immunoassay, while example 7 teaches a no wash immunoassay.

It would have been prima facie obvious to modify the immobilization of the bacteria to a solid surface using polylysine using a for detecting the presence of specific microorganisms having characteristic resonance enhanced Raman backscattered energy spectrum with the immobilization technique using an antibody as taught by Taracha et al; who teach immobilization of an analyte with antibody and performing Raman analysis. One would expect reasonable success by exchanging polylysine immobilization for site-specific immobilized antibodies when both techniques are specifically used to immobilize an analyte for Raman analysis and both techniques are known to be compatible with Raman analysis, when Tarcha et al., teach that such binding increases specificity in Raman analysis. Moreover, Taracha et al., teach antibody immobilization allows the percentage of capture sites available to be up to 75% or more of the number of capture molecules which increases the sensitivity of the assay.

7. Claims 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. (US 4,487,198) and Tarcha et al., (US Patent 5,266,498), in further view of Muller (US Patent 5,126,244). Nelson et al. (US 4,487,198) and Tarcha et al., (US Patent 5,266,498) have been discussed above, however neither specifically teaches the use of *E. coli* antibodies.

Muller (US Patent 5,126,244) teaches the determination of antigens. Antigens from bacteria for immunological can be found (col. 1 lines 35-40). Example 1 A.3 teaches the qualitative determination of *E. coli* antigens with *E. coli* antibodies used in an enzyme immunoassay.

It would have been prima facie obvious to modify Nelson et al., and Taracha et al., who teach a method for detecting the presence of specific microorganisms, including E.Coli, having characteristic resonance enhanced Raman backscattered energy spectrum by irradiating nucleic acids using solid phase immobilized antibodies wherein the modification is incorporating antibodies against *E. coli*. One would have a reasonable expectation to incorporate the anti-Ecoli antibody as taught by Muller et al., when the prior art already teaches using antibodies to immobilize analyte microorganisms and the prior art teaches subject E. coli to Raman analysis. Moreover, Muller et al., teach qualitative determination of *E. coli* antigens using said antibodies to specifically bind to E. coli.

8. Claims 2, and 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. (US 4,487,198) in view of Tarcha et al., (US Patent 5,266,498). Chadha et al., teach the use of ultraviolet micro-Raman spectrograph for the detection of small numbers of bacterial cells. The application of UV resonance Raman spectroscopy is used to selectively excite taxonomic markers to probe and identify bacteria. (page 3088 para.3). Chadha et al., teach resonance enhancement of the vibrational modes of the bacteria cell components by UV excitation should allow for high selectivity and sensitive analysis of individual components (page 3088 para. 2). "Nucleic acids have a prominent absorption band around 260 nm, consequently it is not surprising Raman spectra with 257 nm excitation would contain several strong resonance enhanced vibrational modes due to nucleic acids." (page 3092 para. 3). The experimental conditions Chadha et al., teach immobilization of the bacterial cells by means of polylysine, including a wash of the immobilized cells to ensure complete

removal of culture medium, and then resuspend the cells in a fluid medium, like phosphate buffer to lower their metabolic activity (page 3091 para. 6). Chadha et al., teach vibrational modes appearing at 1483 cm^{-1} in different bacterial species (*flavobacterium* and *bacillus*) and these spectra show selectively enhanced modes due to the nucleic acids adenine and guanine (page 3092 para. 3 and 5). Chadha et al., also describes the UV micro-Raman spectrograph (page 3090 para. 2).

Tarcha et al., (US Patent 5,266,498) has been discussed above.

It would have been prima facie obvious to modify the immobilization of the bacteria to a solid surface using polylysine using a for detecting the presence of specific microorganisms having characteristic resonance enhanced Raman backscattered energy spectrum as taught by Chadha et al., who teach the benefits of washing cells and for using nucleic acids as markers because they show strong resonance enhanced vibrational modes and provided better signals over the interference in Raman spectroscopy; and using the exact same wavelengths separately, and benefits for using 242nm (because it promises better signal to noise even if Raman cross sections are lower) and 257nm (because it would contain several strong resonance enhanced vibrational modes due to nucleic acids) and that the wavelengths of 242, 252, 257nm are selectively excited for the vibrational modes of various nucleosides and nucleic acids; with the immobilization technique using an antibody as taught by Taracha et al; who teach immobilization of an analyte with antibody and performing Raman analysis. One would expect reasonable success by exchanging polylysine immobilization for site-specific immobilized antibodies when both techniques are specifically used to immobilize an analyte for Raman analysis and both techniques are known to be compatible with Raman analysis, when Tarcha et al., teach employing immobilized

antibodies that would increase the sensitivity of the assay while such binding increases specificity in Raman analysis. Moreover, Taracha et al., teach antibodies can be used with Raman analysis to provide microorganism specific analysis and antibody immobilization allows the percentage of capture sites available to be up to 75% or more of the number of capture molecules which increases the sensitivity of the assay.

Response to Arguments

9. Applicants submitted a declaration of Chris Brown, Ph.D. This declaration purportedly teaches that the practice of the claimed method as set forth in claim 9 and 12 yields unexpected results because one of skill in the art would have expected that the irradiation of antibodies and/or antibody-antigen complexes with light having a wavelength in the range of about 242-257nm to produce resonance Raman spectra that would have interfered with the resonance Raman spectra of microorganisms in the sample when practicing the claimed method as set forth in claim 9 or using the claimed system as set forth in claim 12. The declaration under 37 CFR 1.132 filed January 15, 2002 is insufficient to overcome the rejection of claims 2, 9 and 12-15 because the Declaration merely states that a wavelength in the range of about 242-257 nm to produce resonance Raman spectra that would have interfered with the resonance Raman spectra of microorganisms in the sample; however this statement is unpersuasive.

The declaration fails to address that the molar amount of antibody protein present is insignificant compared to the size of the microbe and the amount of protein present in the microorganism. As such one skilled in the art would not expect interferences at all. Moreover, the Nelson et al., in *UV Resonance Raman Studies of Bacteria* teach the UV resonance Raman studies of whole bacteria cells were

accomplished with 242nm excitation, it was expected that since this wavelength corresponds very nearly to the protein absorption minimum, spectra would contain nucleic acid modes primarily, and indeed, at 242nm, nucleic acid symmetric vibrations were strongly excited along with a few tryptophan and tyrosine modes, see figure 3 showing the 242nm excited spectra of four types of bacteria; thus not unexpectedly an extension of the study lead to spectra excited at 251nm. Spectra obtained at 251nm showed excitation very near to 242nm however all tyrosine contributions are absent in 251nm excited spectra (page 84). Other differences include an attempt to measure the relative cross-sections of the major nucleic acids and amino acid peaks specifically trp, try, G and A, however the spectra as shown in Figure 6 shown a pronounced peak at 1488 cm^{-1}, unlike the bacteria. Furthermore, figure 4 shows the resonance Raman spectra of E.coli excited at the same wavelength, however there appears to be no interference, since intensity peaks are observed at different positions. Therefore, there would have been no expectation of interference because the molecule is comprised of aromatic amino acid and/or antibody-antigen complexes with the claimed ranges. The interpretation of spectra is important, thus it is important to realize that while bacterial spectra can be interpreted in terms of nucleic acids and aromatic amino acid contributions, the cross-section of a peak belonging to a cell is not simply due to the additive contributions of the unassociated components, but rather the whole, thus the whole is more than the sum of parts (page 86-88).

Applicants have furnished exhibits A, B and C which teach that aromatic amino acids produce resonance Raman spectra when irradiated at a wavelength of about 242-257, however, it is noted that none of the reference teach not irradiating at a wavelength of about 242-257 because of interference from the aromatic amino acids.

The declaration fails to explicitly disclose the scientific basis of the "unexpected results". Furthermore, the declaration does not point to relevant art showing a teach away of irradiating at a wavelength of about 242-257 because aromatic amino acids can be excited at that wavelength. Therefore, the declaration failed to provide evidence of unexpected results.

The statement of possible interference neither teach away nor conforms an ineffective result achieved from the combination of cited prior art. Thus the statement that unexpected results have been achieved is not commensurate with the scope of the claims.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is

(703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines
May 1, 2002

PATRICIA A. DUFFY
PRIMARY EXAMINER